Phase I trial of the CDK4/6 inhibitor, P1446A-05 in combination with the BRAF inihibitor, Vemurafenib in BRAF mutant melanoma

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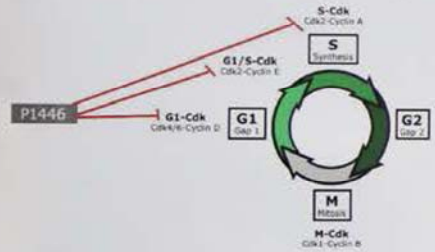
Background

- P1446A-05 is a potent, selective CDK4/6 inhibitor with activity in multiple BRAF mutant and wild type cell lines.
- The BRAF inhibitors have been transformative in the therapy of *BRAF V600* mutant melanoma.
- Resistance to BRAF inhibitors does develop frequently, often in a few months..
- Increased cyclin D1 which stimulates CDK4/6 mediates BRAF inhibitors resistance in *BRAF V600* mutant melanoma.
- The addition of a CDK 4/6 inhibitor delayed the onset of BRAF inhibitor resistance in preclinical study.



Methods

- A prospective, multicenter Phase I trial was conducted to determine the safety, maximum tolerated dose (MTD) and dose limiting toxicity of P1446A-05 in combination with Vemurafenib.
- The Phase I dose escalation part of the trial is reported here.
- A total of 4 cohorts were planned in the Vemurafenib-arm of this phase in the trial.
- Vemurafenib was escalated starting with a dose of 720 mg PO BID and P1446A-05 was planned to escalate starting with 150 mg up to 350 mg PO QD.
- In each cohort, 3 to 6 patients were planned to be enrolled.
- Extensive PK analysis was conducted.
- Eligible patients could be BRAFi-naïve or resistant, ECOG PS 0-1, and QTc < 480 at baseline.

Results

Table 1. Patients Characteristics

Variable	Patients (N=9)
Mean Age (range)	44.7 (32-59)
Gender	
Male	8
Female	1
Stage	
M1a	5
M1b	2
M1c	2
Previous treatment	
BRAFi Naïve	3
BRAFi refractory	6

Table 2. Previous treatment and sites of disease

Cohort	Patient	Previous systemic treatment	Sites of disease
Cohrot I vemurafenib 720mg BID + PA1446A-05 150mg/d	1101	vemurafenib, dabrafenib	LN
	1201	none	lung
	1202	vemurafenib, dabrafenib + trametinib	LN
Cohrot II vemurafenib 960mg BID + PA1446A-05 150mg/d	1103	dabrafenib plus trametinib	LN, lung
	1203	vemurafenib, dabrafenib + trametinib	cutaneous, LN
	1204	dabrafenib + trametinib	LN, liver
	1205	none	cutaneous
	1105	none	cutaneous, LN, liver
	1106	vemurafenib + cobimetinib, pembrolizumab	cutaneous

Table 3. Mean(%CV) PK Parameters of P1445A-05

Parameter	C1D15	C1D19
Dose	150mg	150mg
C_{max}	796ng/ml (51%) 1.7μM	639ng/ml (41.2%) 1.36μM
AUC_{0-8}	5315hr × ng/ml (49.6%)	4288hr × ng/ml (44%)
AUC_{0-24}	14451hr × ng/ml (61.5%)	12384hr × ng/ml (48%)
T_{max}	4hr	2hr

Table 4. Mean(%CV) PK Parameters of Vemurafenib

Parameter	C1D15	C1D19
Dose	720mg	720mg
C_{max}	52,600ng/ml (51%) 107μM	58,800ng/ml (41.2%) 120μM
AUC_{0-8}	337,467hr × ng/ml (51.9%)	370,467hr × ng/ml (32.2%)
AUC_{0-24}	1067,333hr × ng/ml (55.7%)	1158,733hr × ng/ml (25.1%)
T_{max}	2hr	pre-dose

Table 5. Adverse events

Adverse Event	Cohrot 1 (N=3)		Cohort 2 (N=6)		total (N=9)
	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4	
Photophobia	1 (33.3%)	0	0	0	1 (11.1%)
Constipation	2 (66.7%)	0	1 (16.7%)	0	3 (33.3%)
Diarrhea	2 (66.7%)	0	1 (16.7%)	0	3 (33.3%)
Nausea	1 (33.3%)	0	1 (16.7%)	0	2 (22.2%)
Vomiting	1 (33.3%)	0	1 (16.7%)	0	2 (22.2%)
Fatigue	1 (33.3%)	0	2 (33.3%)	1 (16.7%)*	4 (44.4%)
Infection	1 (33.3%)	0	0	0	1 (11.1%)
alkaline phosphatase increase	0	0	1 (16.7%)	0	1 (11.1%)
Blood bilirubin increase	1 (33.3%)	0	0	0	1 (11.1%)
Decreased appetite	1 (33.3%)	0	1 (16.7%)	0	2 (22.2%)
Hyperglycemia	1 (33.3%)	0	0	0	1 (11.1%)
Arthralgia	2 (66.7%)	0	1 (16.7%)	0	3 (33.3%)
Arthritis	0	0	1 (16.7%)	0	1 (11.1%)
Back pain	1 (33.3%)	0	0	0	1 (11.1%)
Groin pain	1 (33.3%)	0	0	0	1 (11.1%)
Myalgia	1 (33.3%)	0	0	0	1 (11.1%)
Pain in extremity	0	0	1 (16.7%)	0	1 (11.1%)
Dysgeusia	0	0	1 (16.7%)	0	1 (11.1%)
Headache	3 (100%)	0	0	0	3 (33.3%)
Neuropathy peripheral	1 (33.3%)	0	0	0	1 (11.1%)
Anxiety	1 (33.3%)	0	0	0	1 (11.1%)
Pollakiuria	0	0	1 (16.7%)	0	1 (11.1%)
Dyspnea	1 (33.3%)	0	0	0	1 (11.1%)
Nasal congestion	1 (33.3%)	0	0	0	1 (11.1%)
Throat irritation	0	0	1 (16.7%)	0	1 (11.1%)
Dry skin	1 (33.3%)	0	0	0	1 (11.1%)
Photosensitivity reaction	0	0	2 (33.3%)	0	2 (22.2%)
Pruritus	1 (33.3%)	0	1 (16.7%)	0	2 (22.2%)
Rash	1 (33.3%)	0	0	0	1 (11.1%)

* grade 3 toxicity

Table 6. Individual patient response

Cohort	Patient	Objective Clinical Response cycle 2	cycle 4	cycle 10
Cohrot I vemurafenib 720mg BID + PA1446A-05 150mg/d	1101	PD		
	1201	CR	CR	CR
	1202	PD		
Cohrot II vemurafenib 960mg BID + PA1446A-05 150mg/d	1103	PD		
	1203	PD		
	1204	PD		
	1205	PR	PR	
	1105	PR	PR	
	1106	PD		

Table 7. Summary of clinical response

	Overall Response	CR	PR
All (N=9)	3 (33%)	1 (11%)	2 (22%)
BRAFi naive (N=3)	3 (100%)	1 (33%)	2 (66%)

Summary

- A total 9 patients have been accrued. Among them, 3 patients were BRAF inhibitor naïve and 6 were BRAF inhibitor refractory.
- The treatment was well-tolerated without significant drug-drug interaction.
- Most common adverse events are fatigue (4), constipation (3), diarrhea (3), arthralgia (3) and headache (3).
- 1 DLT has been observed (grade 3 fatigue).
- Responses were observed in all 3 BRAFi navie patients (1 CR and 2 PR).

Conclusions

- The combination of P1446A-05 and Vemurafenib is well tolerated.
- The MTD was not reached in the trial.
- No drug-drug interactions were observed and the PK parameters for the combination were acceptable.
- Preliminary evidence of efficacy in the treatment-naive patients was seen.